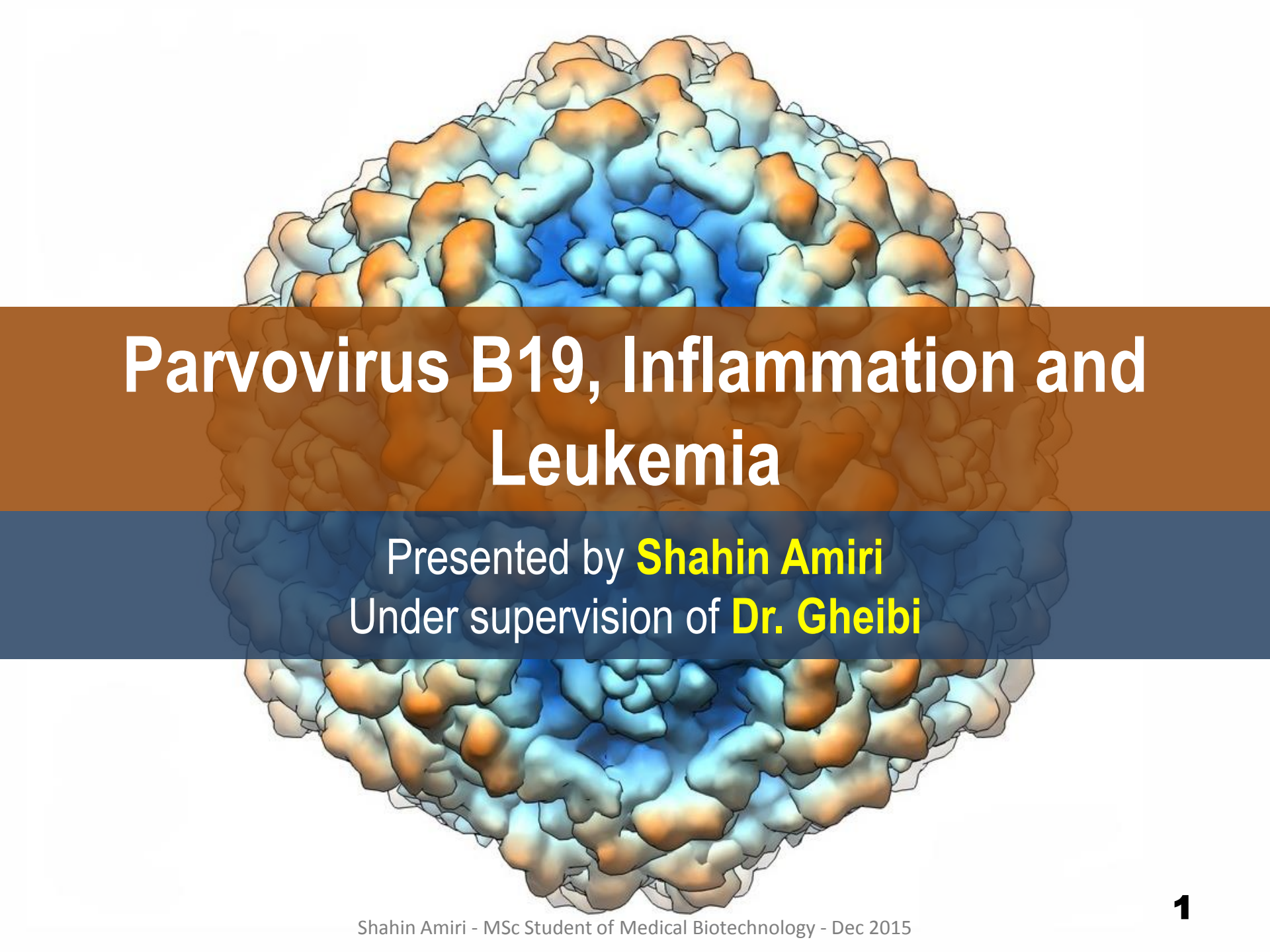
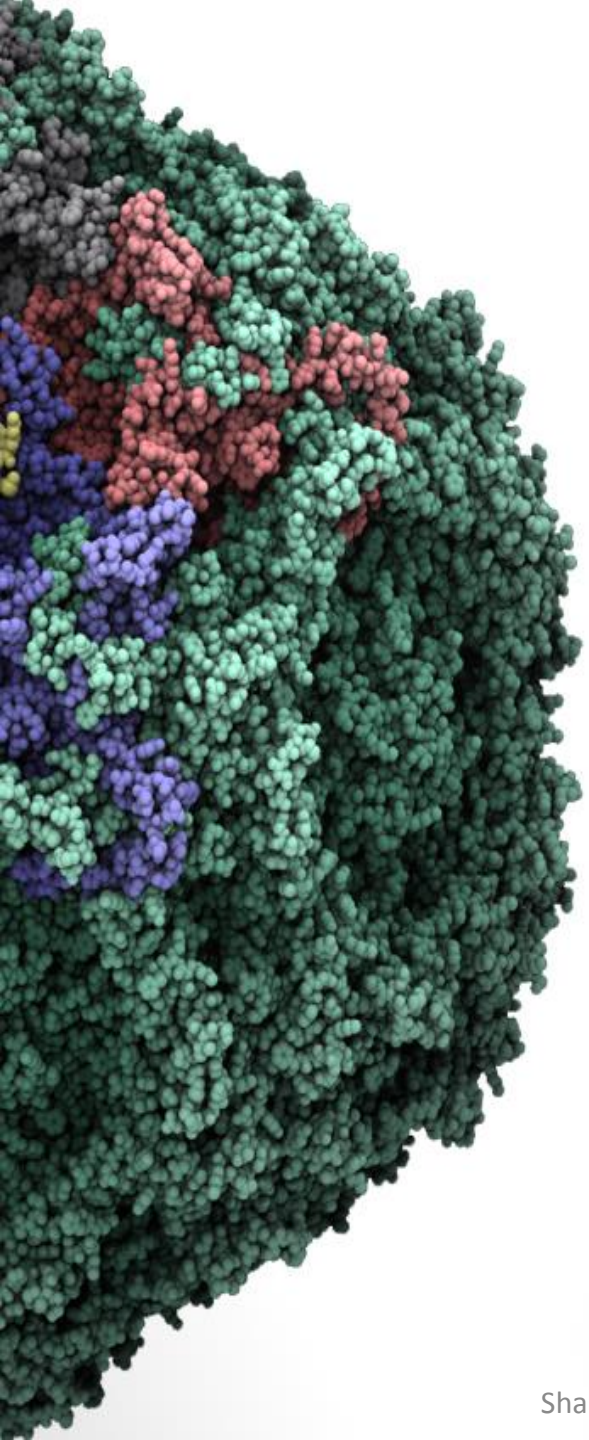


Parvovirus B19, Inflammation and Leukemia

Presented by **Shahin Amiri**
Under supervision of **Dr. Gheibi**



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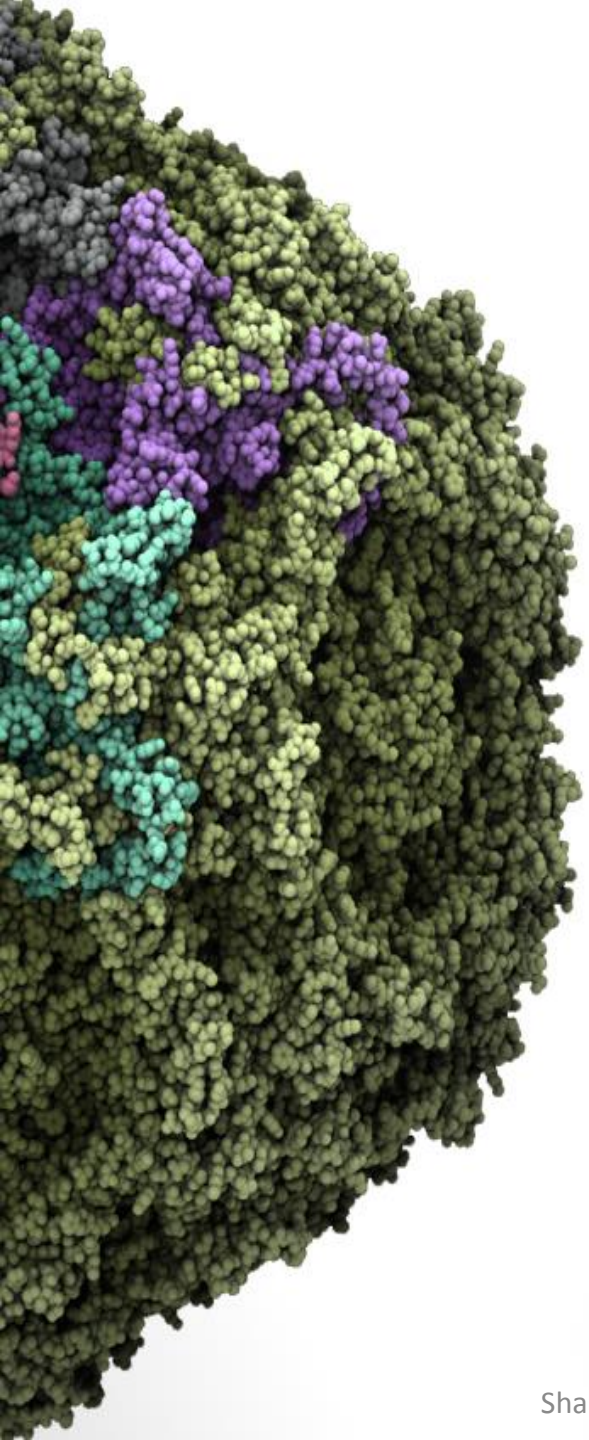
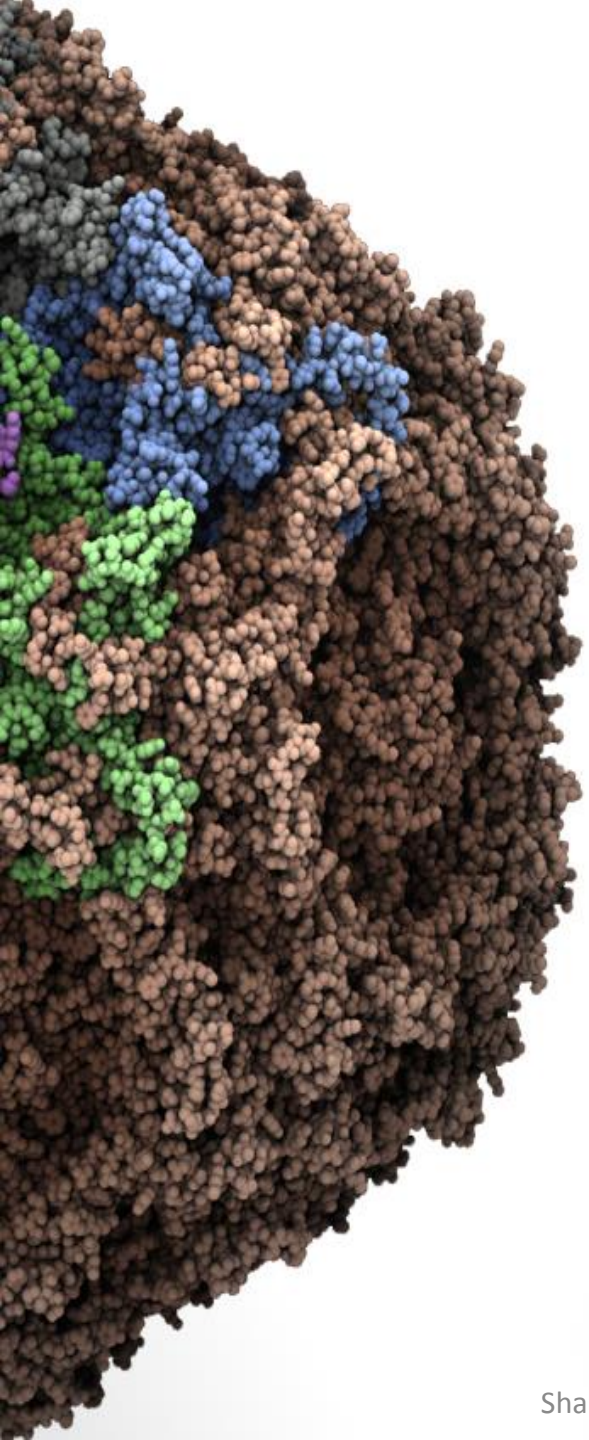


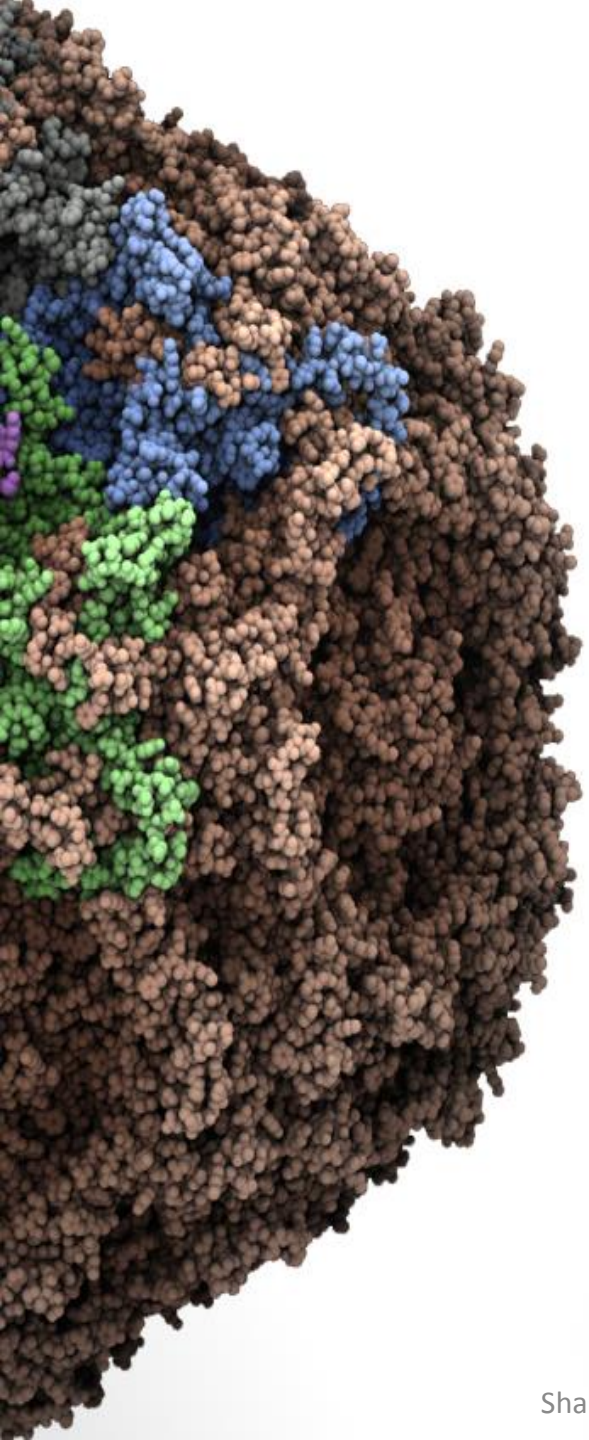
Cancer

- **WHO** estimates for 2011: cancer, more deaths than all coronary heart disease or all stroke **[1]**.
- Example: Leukaemia, 3.2% of all deaths.
- Highest in Northern America and Australia/New Zealand.
- Africa, partly due to failure to diagnose **[2]**.



Inflammation, Tumors and Viruses

- The **link** between **chronic inflammation** and **cancer**: pioneering work of Rudolf Virchow (1863).
- Up to 20% of all human cancers.
- Critical roles: proinflammatory cytokines, tumor-infiltrating myeloid and immune cells.
- Initiation, promotion and progression to malignant metastasis **[3]**.



Inflammation, Tumors and Viruses

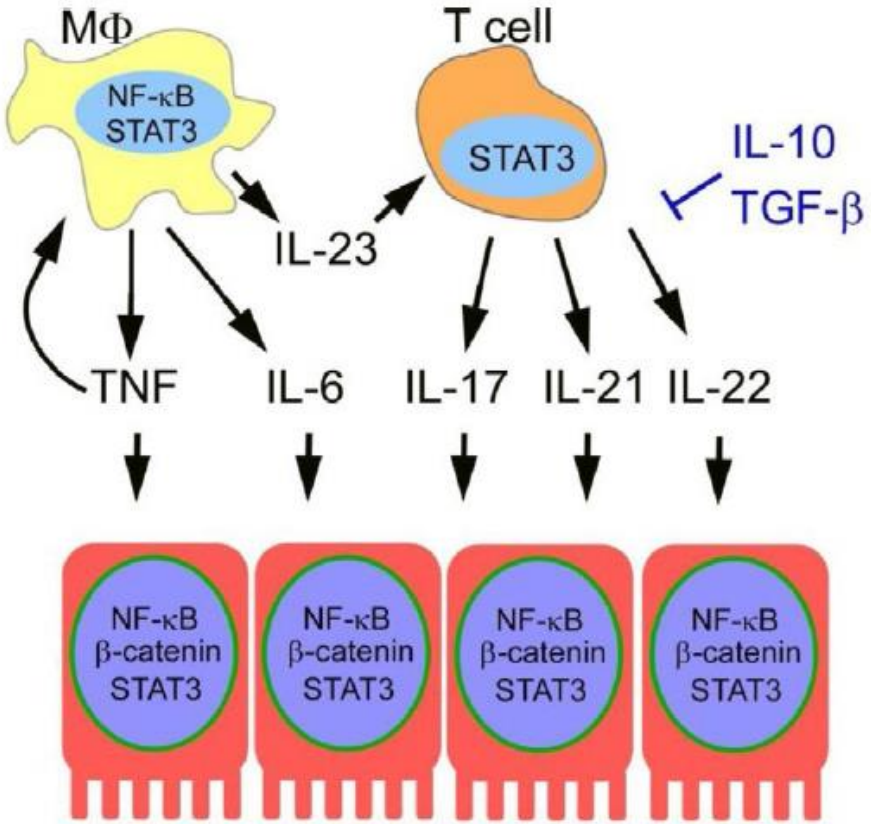
- Even in **cancers** with **no preceding inflammation**: tumor stroma infiltration and cancer development by inflammatory cells.
- Many cytokines:

  Inflammatory: TNF, IL-6,17,21,22,23

  Signals: STAT3, NF-κB

  Anti-inflammatory: IL-10, TGF-β **[3]**.

Mechanism

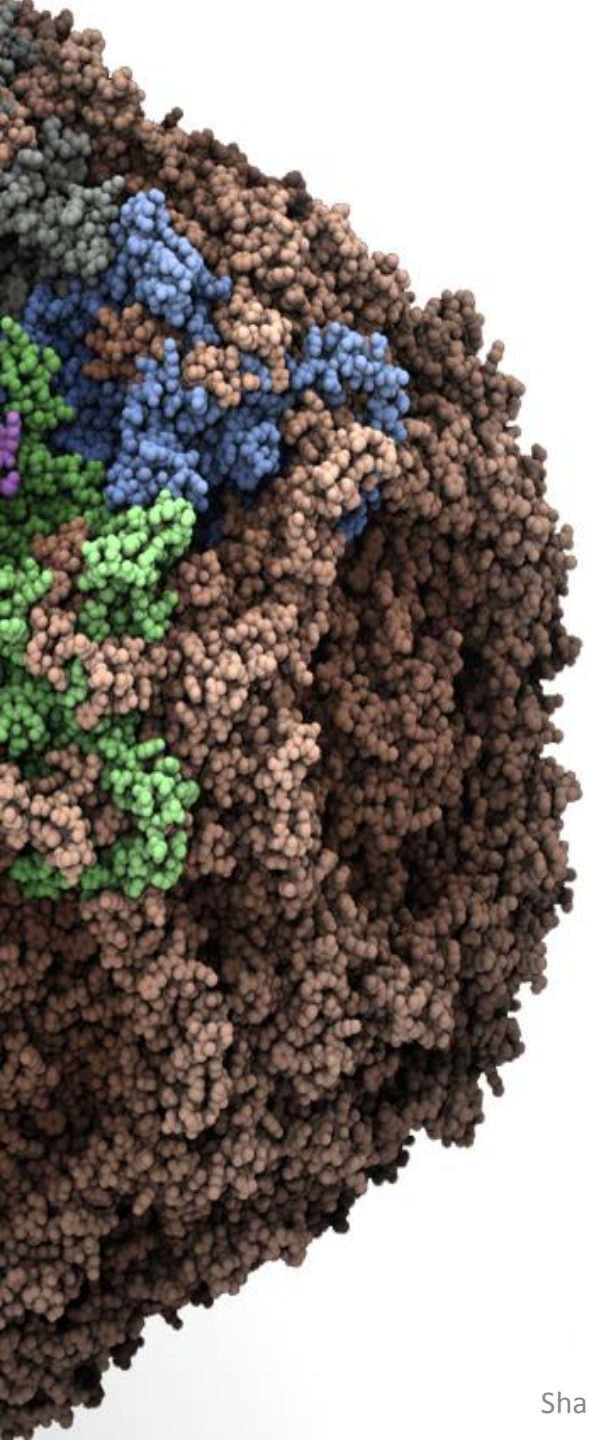


Wang, K. and M. Karin (2015). "Tumor-Elicited Inflammation and Colorectal Cancer." Advances in Cancer Research.

Key Mediators Linking Inflammation and Cancer

Signaling molecules	Role in inflammation-associated cancer
Proinflammatory cytokines	Overexpressed in inflamed, hyperplastic, metaplastic tissues and adenocarcinomas Induce DNA damage Stimulate inflammatory angiogenesis through production/expression of proangiogenic molecules, such as VEGF, VEGFR, IL-8, NO, ICAM-1 and VCAM-1 Activate proinflammatory signaling mediated via JAK-STAT and NF-κB and help to maintain inflammatory tumor microenvironment Stimulate cell proliferation and inhibit apoptosis
Chemokines	Attract inflammatory and immune cells to the tumor microenvironment Promote tumor cell migration and facilitate invasion and metastasis Enhance extravasation of tumor cells through stromal tissue Stimulate inflammatory angiogenesis by upregulating proangiogenic factors, such as VEGF and MMP
COX-2	Catalyzes biosynthesis of lipid mediators of inflammation Helps to maintain a persistent inflammatory state in the premalignant and malignant lesion Overexpressed in various inflammation-associated cancers Promotes cell proliferation and block apoptosis Accelerates angiogenic process by triggering PGE_2 signaling and expression of VEGF and stabilization of HIF-1α
PGE_2	Promotes tumorigenesis in experimental animals Excessively produced as a consequence of COX-2 induction in inflamed, hyperplastic, and dysplastic tissues, and carcinomas Augments cell proliferation, suppresses apoptosis Induces proangiogenic factors and promotes inflammatory angiogenesis Activates proinflammatory signaling pathway with in the tumor microenvironment
iNOS	Is elevated in precancerous and cancerous lesions Induces nitrosative or oxidative DNA damage Produces proinflammatory mediators, e.g., NO, by catalyzing arginine metabolism Acts as a downstream effector of NF-κB and inflammatory cytokine-mediated signaling
NO	Promotes tumor growth by stimulating cell proliferation Causes *S*-nitrosylation of important proteins involved in inflammation and cancer Causes DNA damage by nitration of nucleotide bases
NF-κB	Increases expression/production of proinflammatory mediators and amplifies the inflammatory signal transduction Augments the expression of antiapoptotic proteins and helps transformed cells to escape apoptosis Promotes invasion and metastasis

Kundu, J. K. and Y.-J. Surh (2008). "Inflammation: gearing the journey to cancer." Mutation Research/Reviews in Mutation Research 659(1): 15-30.



Inflammation, Tumors and Viruses

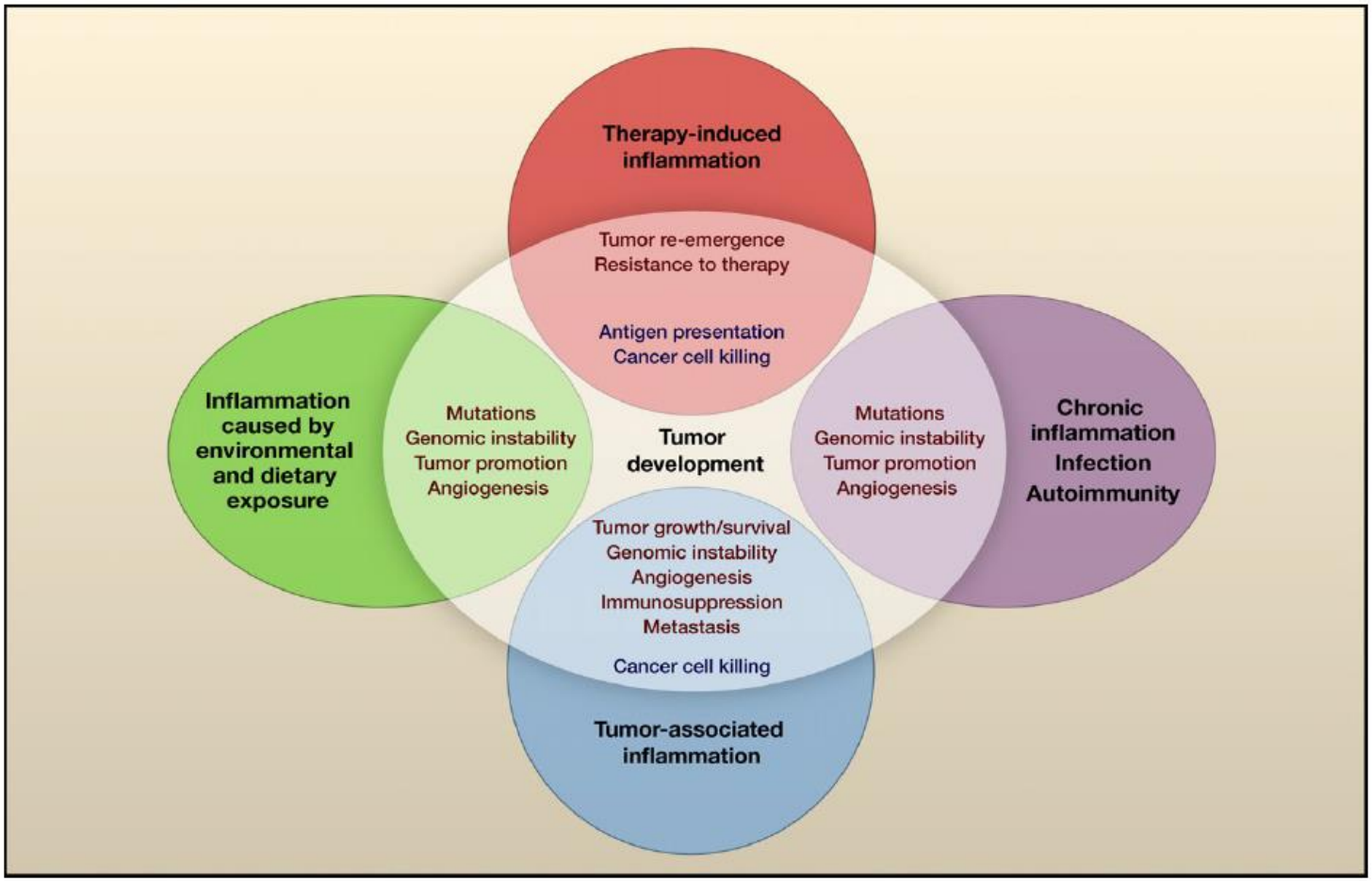
- **Signaling pathways** of protumorigenic effects of **inflammation**: feed-forward loop [4].

NF-kB activation in immune cells

Cytokines Production that activate NF-kB in cancer cells

Chemokines that attract more inflammatory cells

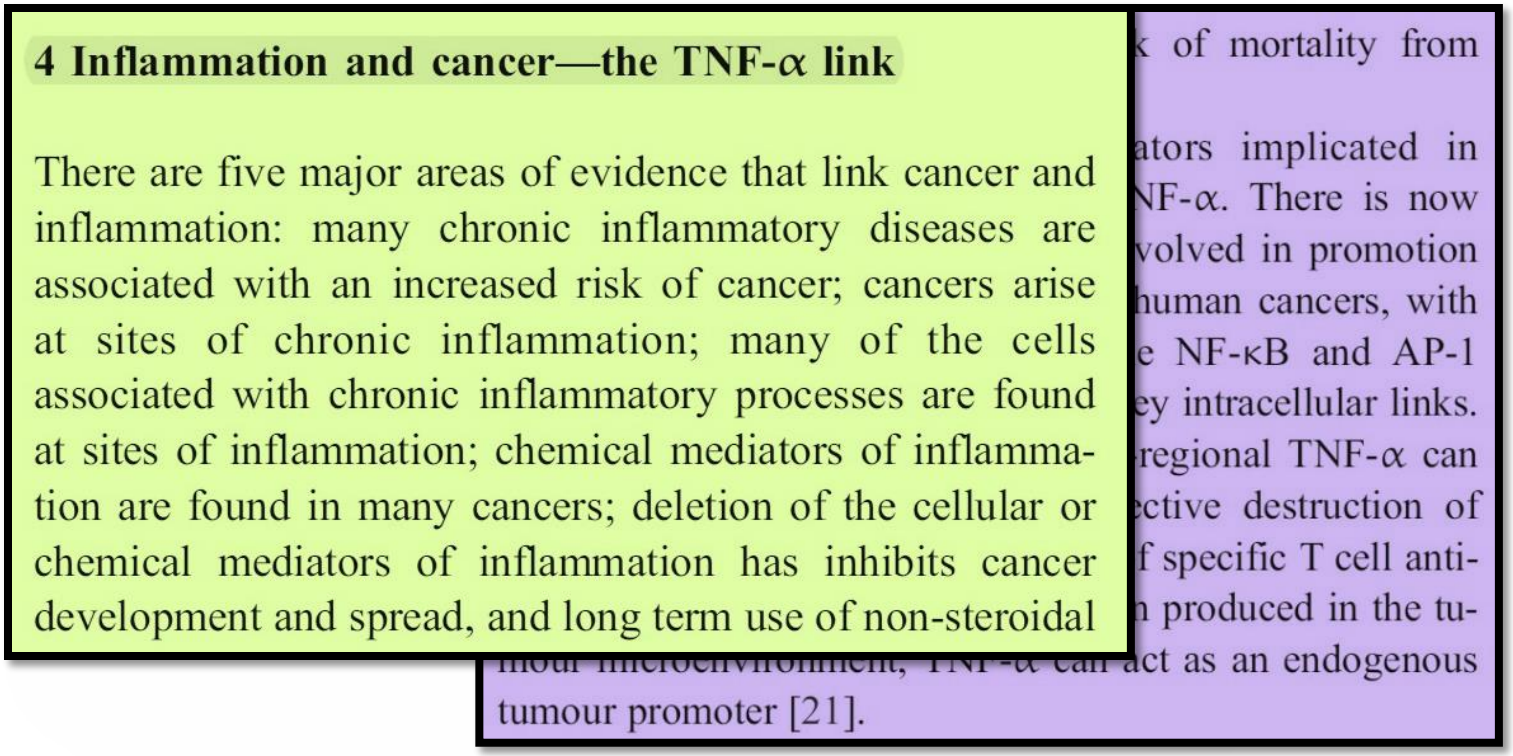
Inflammation, Tumors and Viruses



Grivennikov, S. I., et al. (2010). "Immunity, inflammation, and cancer." Cell 140(6): 883-899.

Inflammation, Tumors and Viruses

- **TNF-α Link** [5].



4 Inflammation and cancer—the TNF-α link

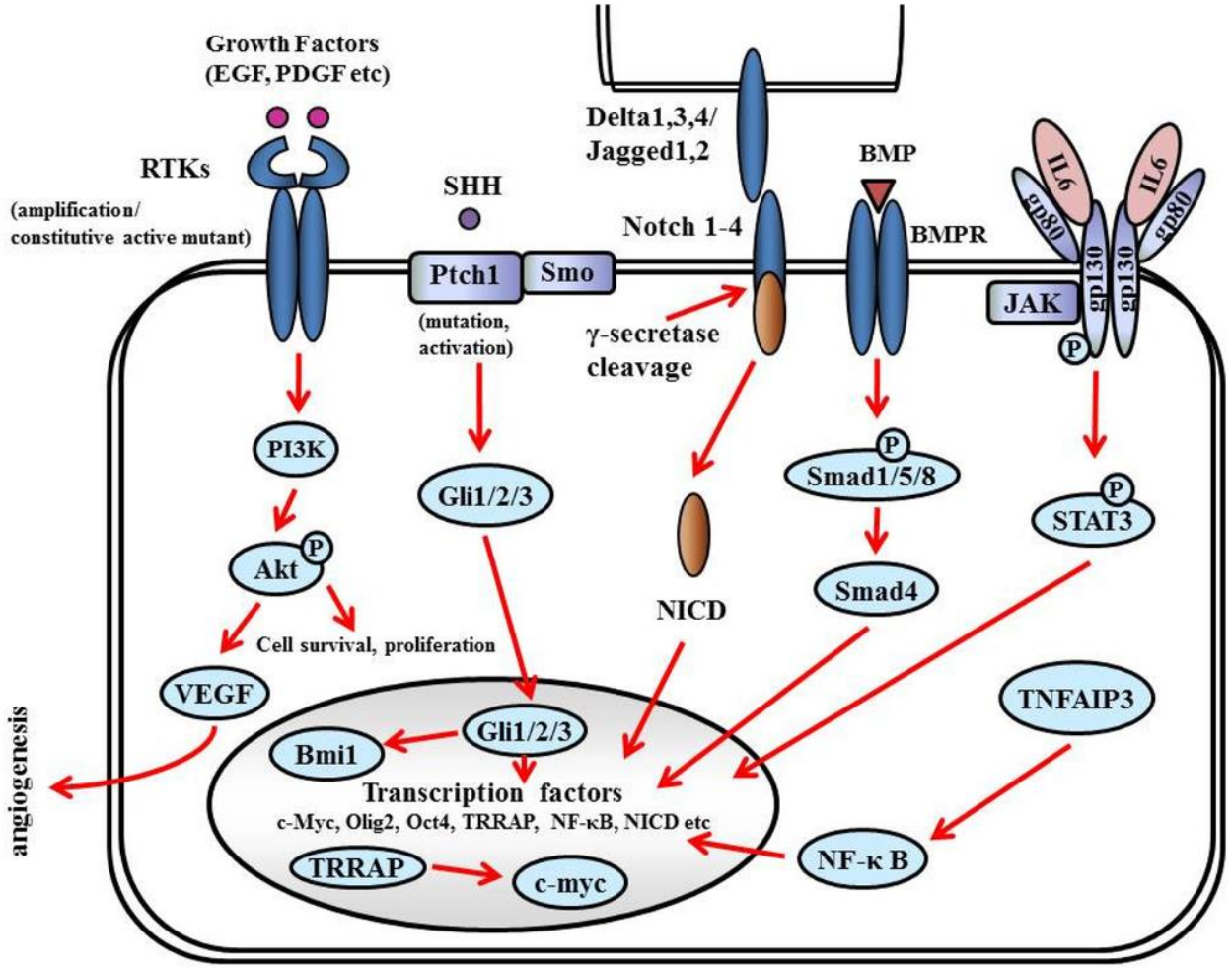
There are five major areas of evidence that link cancer and inflammation: many chronic inflammatory diseases are associated with an increased risk of cancer; cancers arise at sites of chronic inflammation; many of the cells associated with chronic inflammatory processes are found at sites of inflammation; chemical mediators of inflammation are found in many cancers; deletion of the cellular or chemical mediators of inflammation has inhibits cancer development and spread, and long term use of non-steroidal

k of mortality from

ators implicated in
NF-α. There is now
volved in promotion
human cancers, with
e NF-κB and AP-1
ey intracellular links.
regional TNF-α can
ective destruction of
f specific T cell anti-
n produced in the tu-
act as an endogenous
tumour promoter [21].

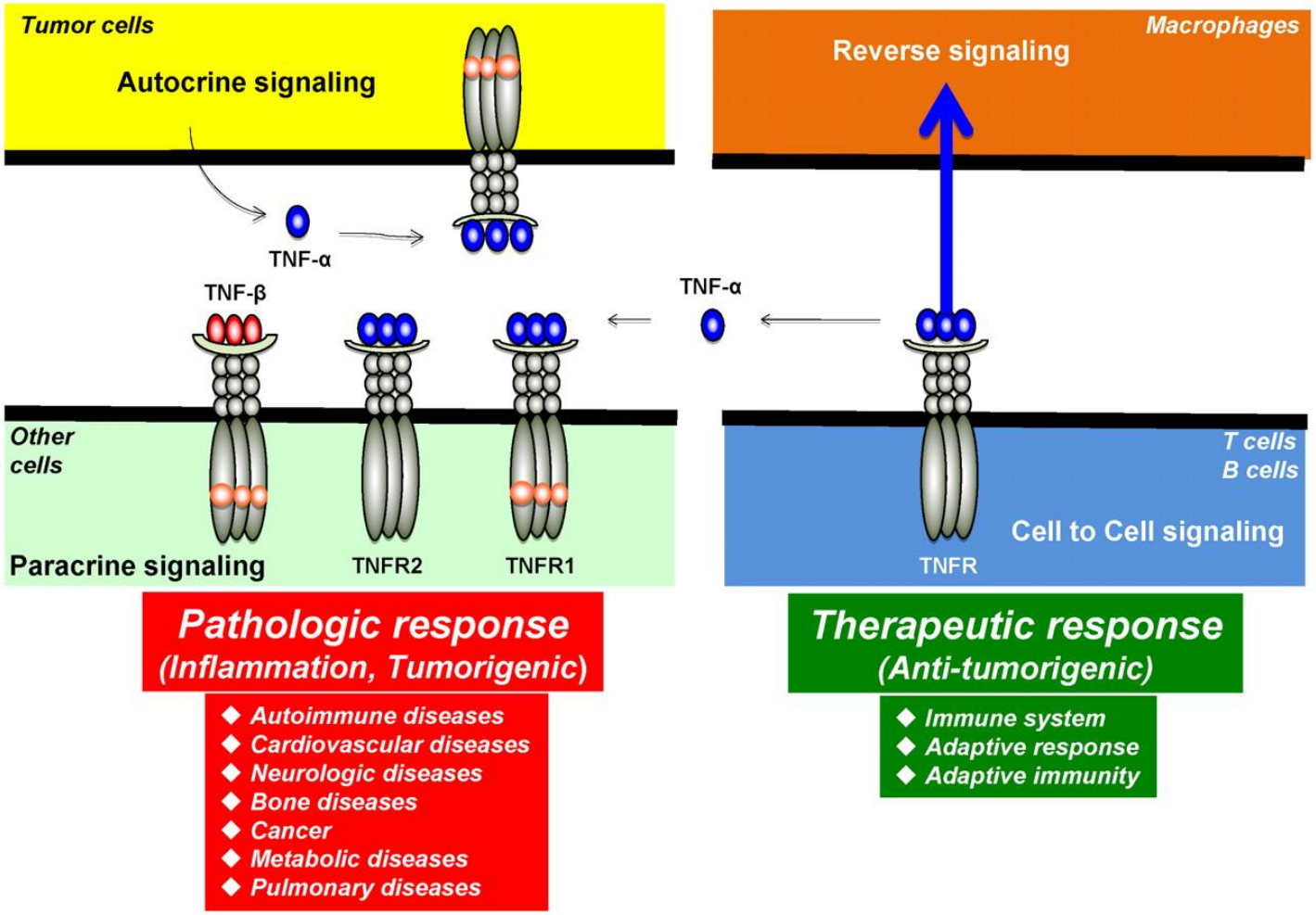
Balkwill, F. (2006). "TNF-α in promotion and progression of cancer." Cancer and Metastasis Reviews 25(3): 409-416.

Tumor Signals



http://www.mdpi.com/2072-6694/3/3/3242/htm

TNF-α



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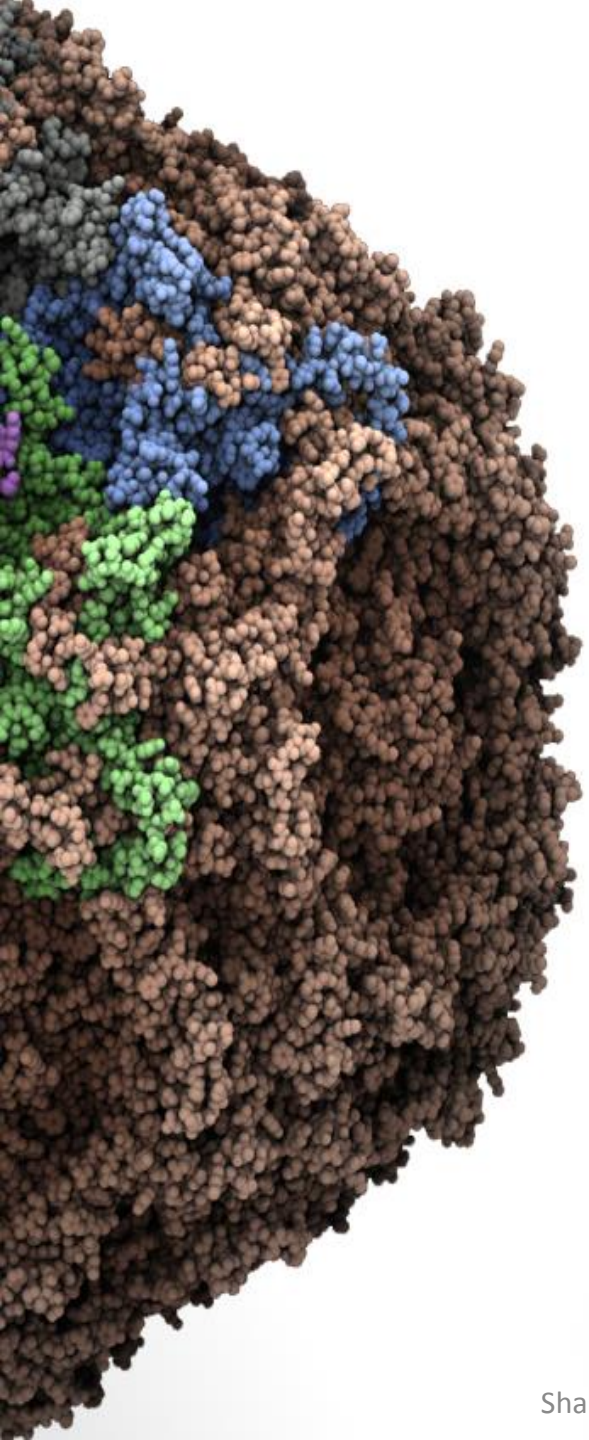


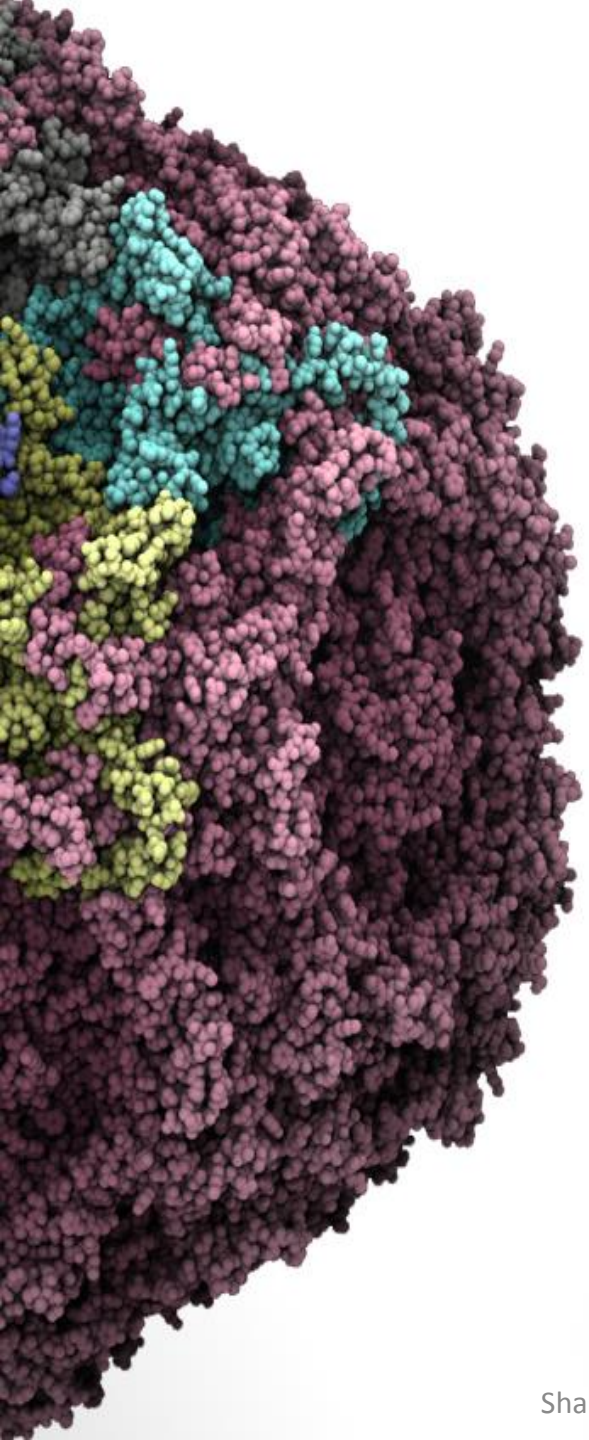
Inflammation, Tumors and Viruses

- **Infection**, most important cause of cancer (2009) **[7]**.

- **Oncogenic Viruses:**

HTLV-1, HPV, HHV-8, EBV, HBV, HCV

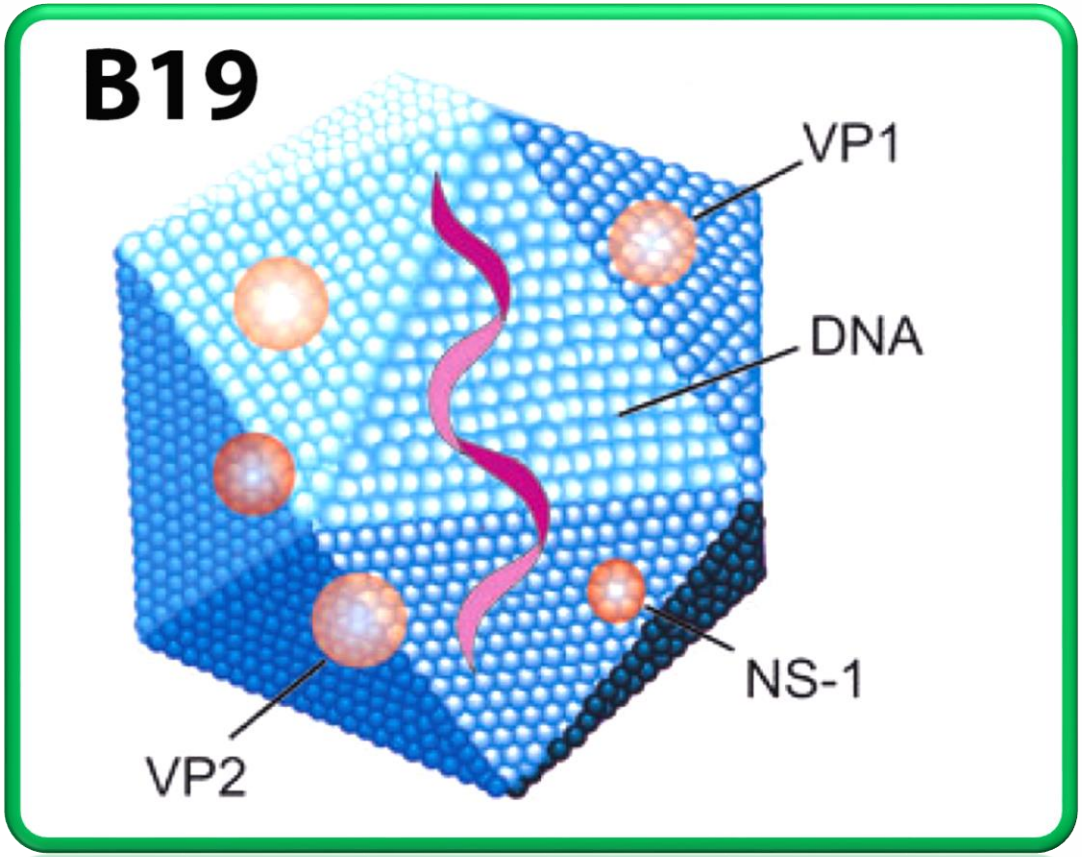
- Epigenetic changes.
- Genomic DNA methylation **[8-19]**.
- **Parvovirus B19**



Parvovirus B19

- **Human PVB19:** small, non-enveloped, icosahedral, ssDNA, 5.6 kb, ITRs (3’ and 5’).
- *Erythrovirus*, the only member of Parvoviridae family causing human diseases.
- Transmission: through the respiratory route.
- Entering: EPCs (CD36+) through P antigen **[22-23]**.

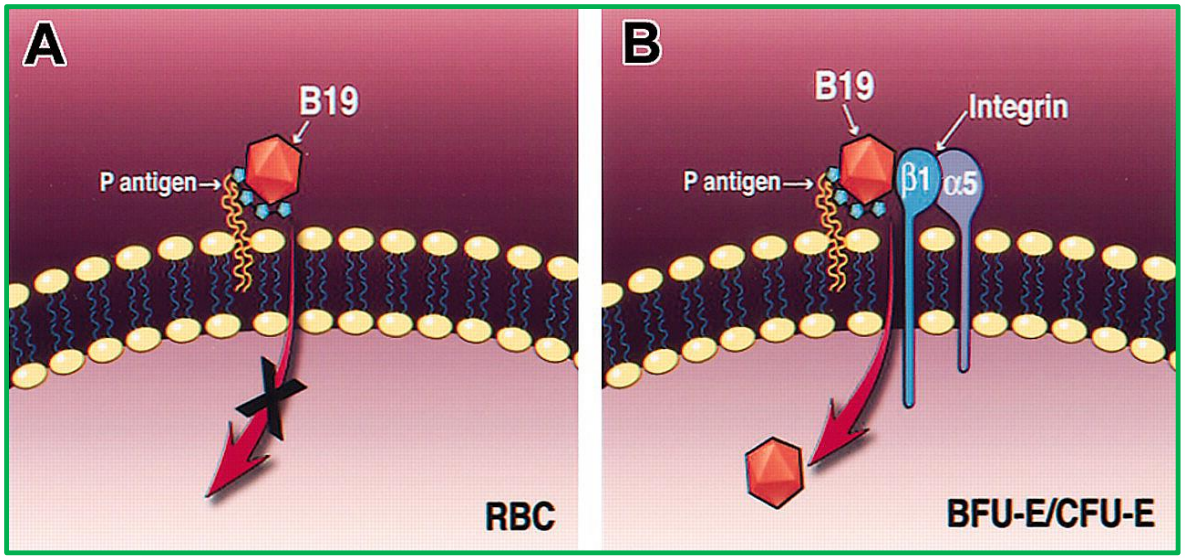
Parvovirus B19



Broliden, K., et al. (2006). "Clinical aspects of parvovirus B19 infection." Journal of internal medicine 260(4): 285-304.

Parvovirus B19

- P antigen (globoside)



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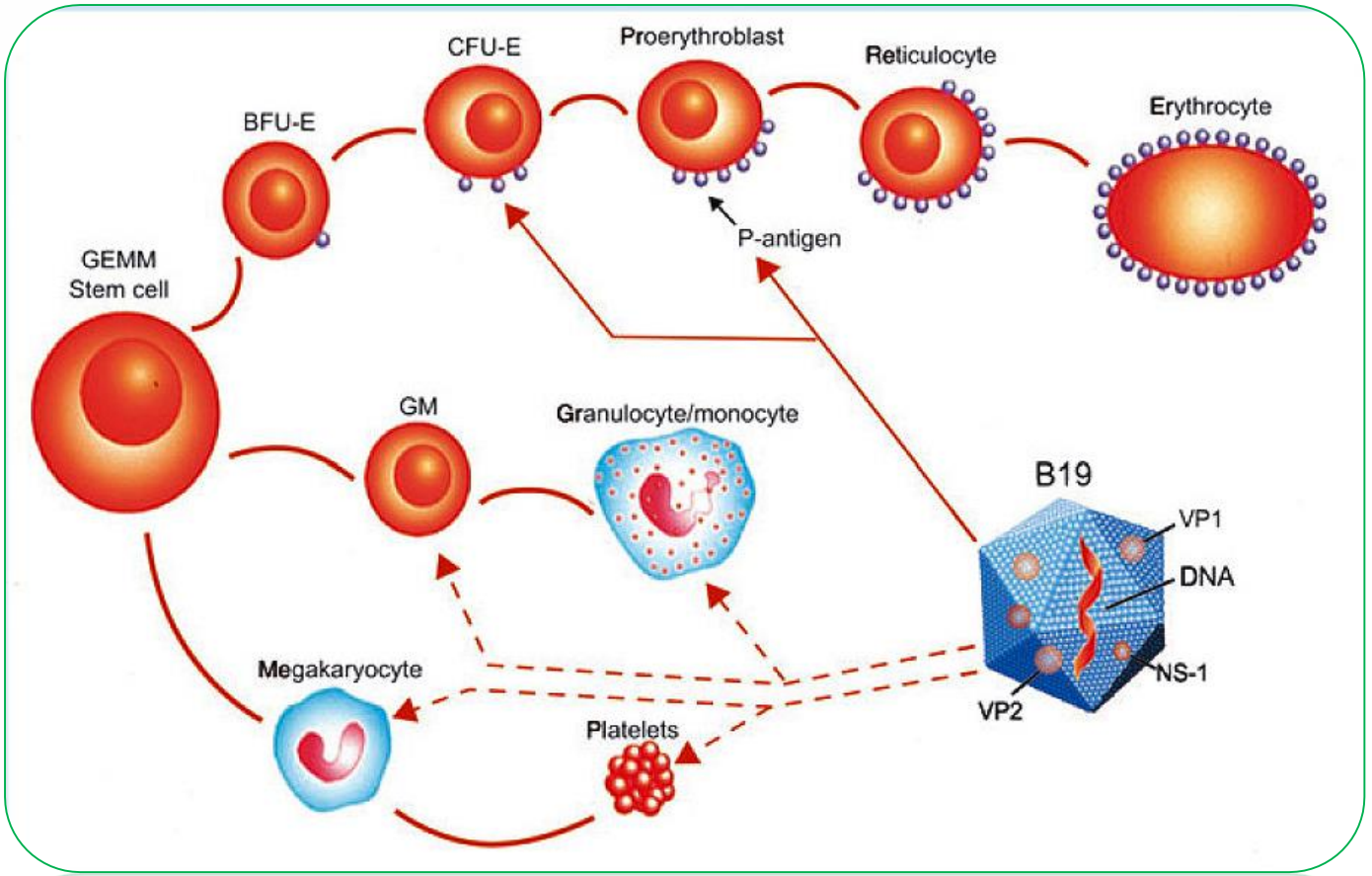
Parvovirus B19



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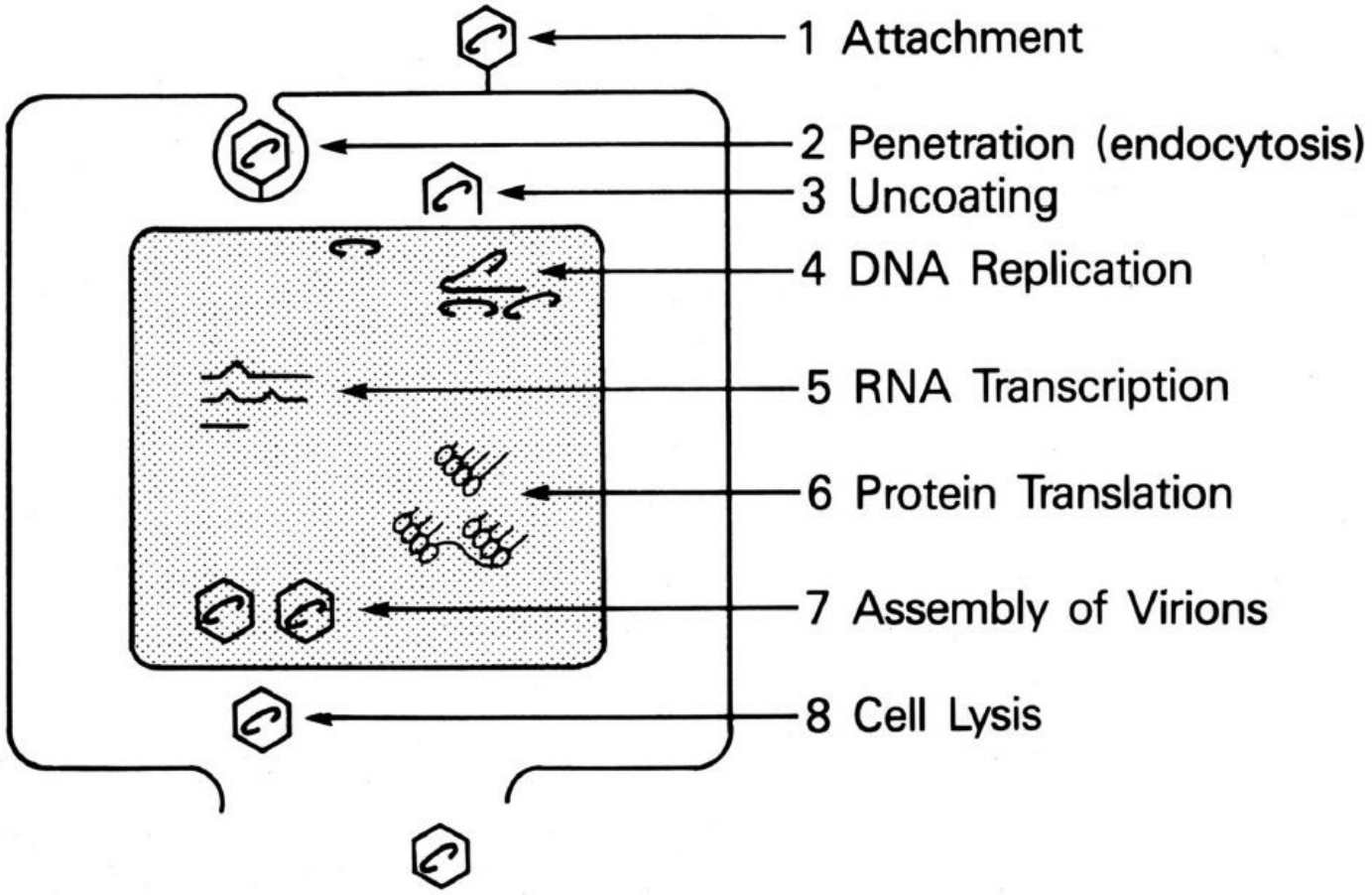
Parvovirus B19



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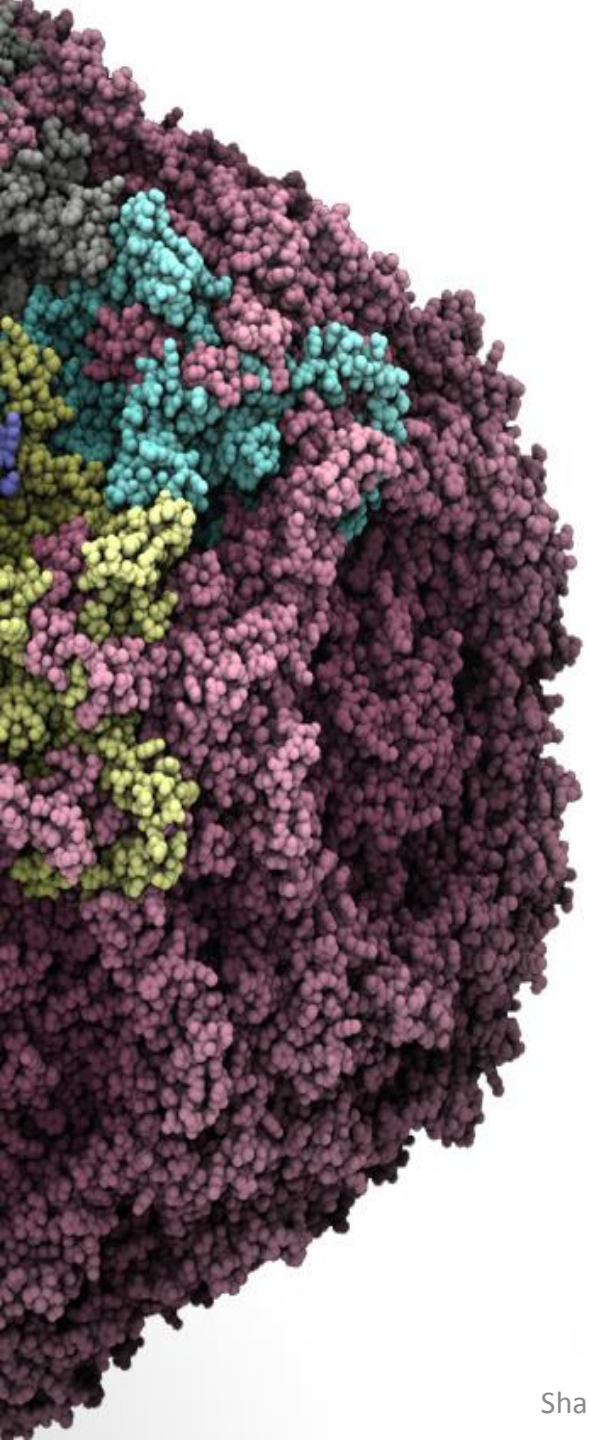
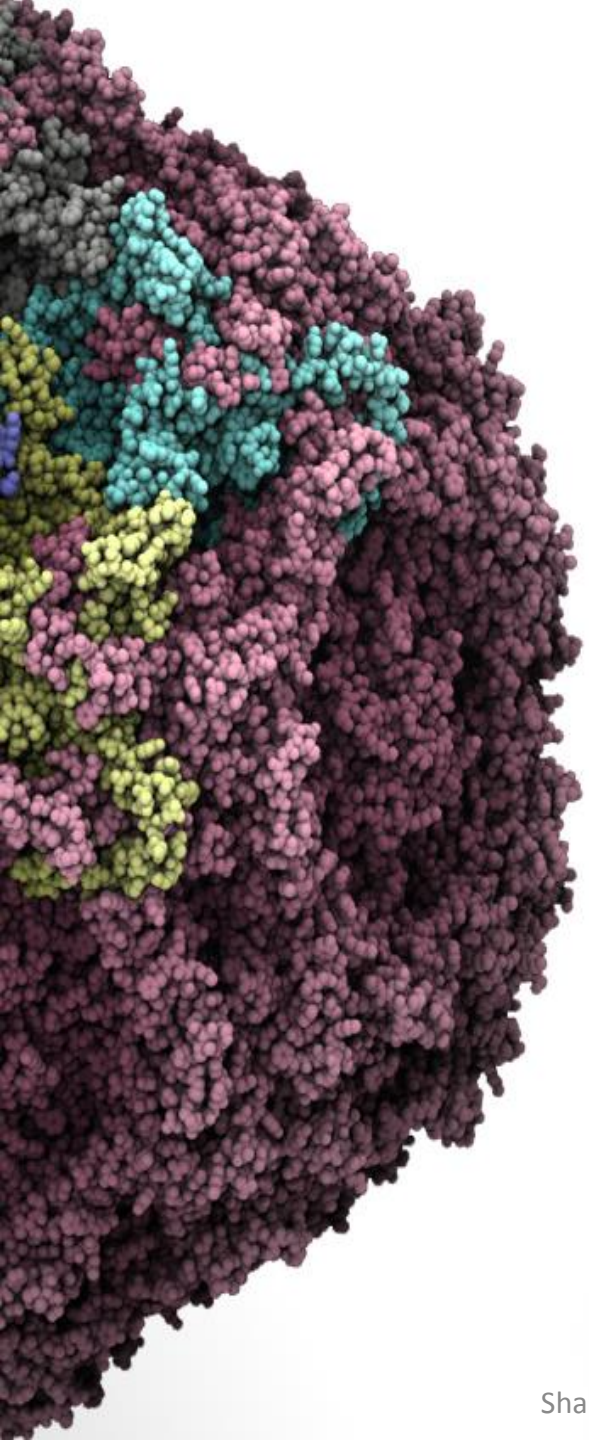


Parvovirus B19 [24]

- Erythema infectiosum
- Hydrops fetalis
- Anaemia
- Pancytopenia
- Transient aplastic crisis
- Arthritis
- Myocarditis
- Hepatitis
- Vasculitis
- CNS (Encephalitis, Meningitis, Peripheral neuropathy)



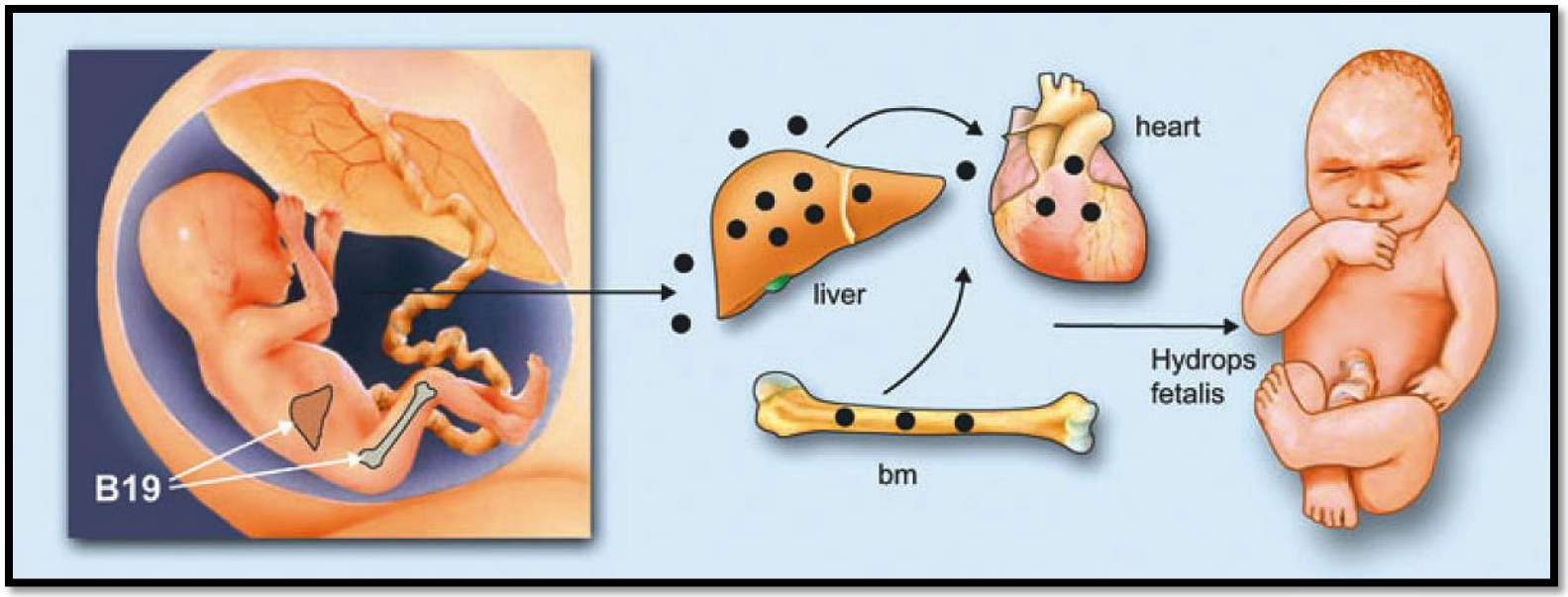
Parvovirus B19

Erythema Infectiosum (Fifth disease)

https://lookfordiagnosis.com/news.php?lang=1&term=Erythema+Infectiosum

Parvovirus B19

Hydrops fetalis



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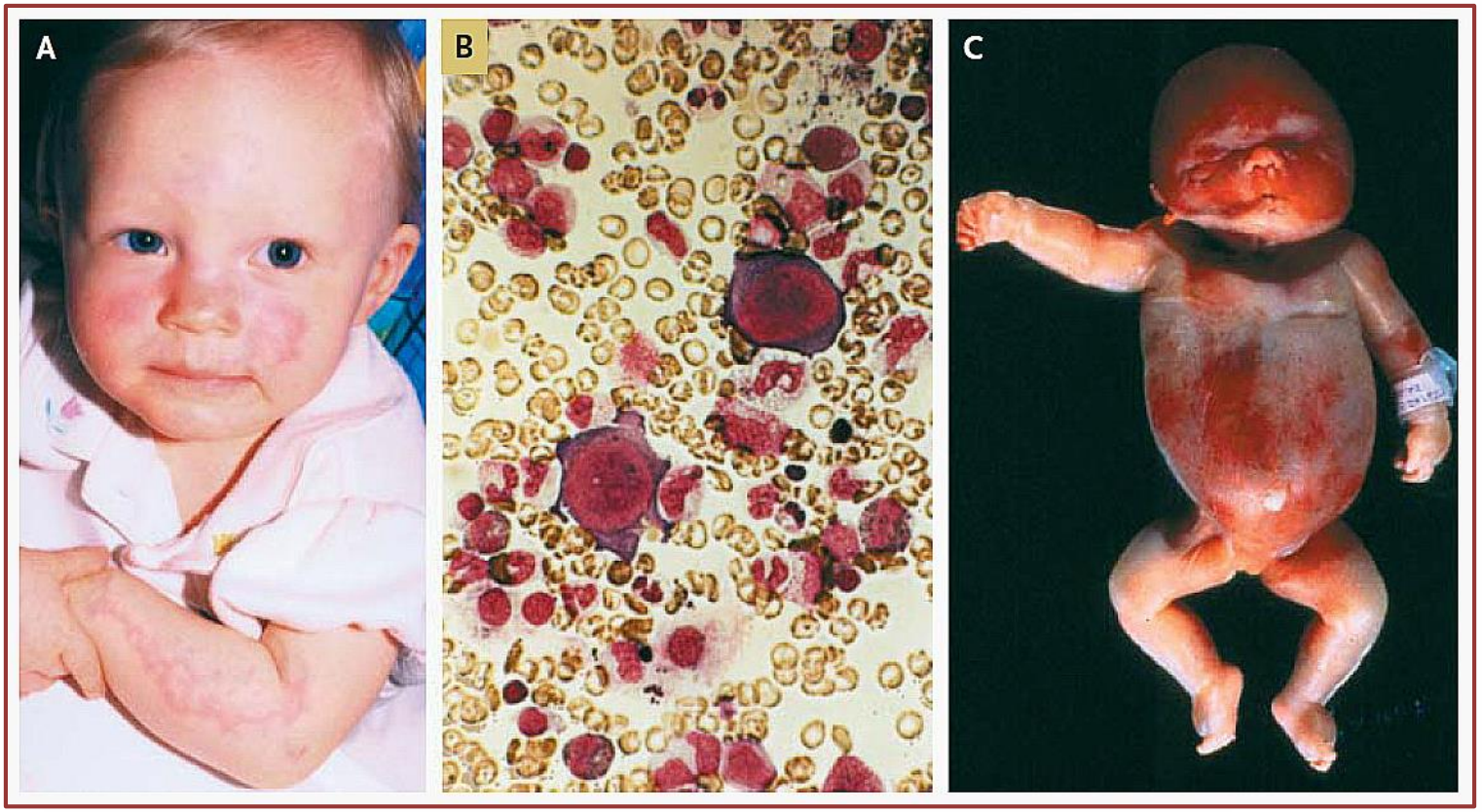
Parvovirus B19



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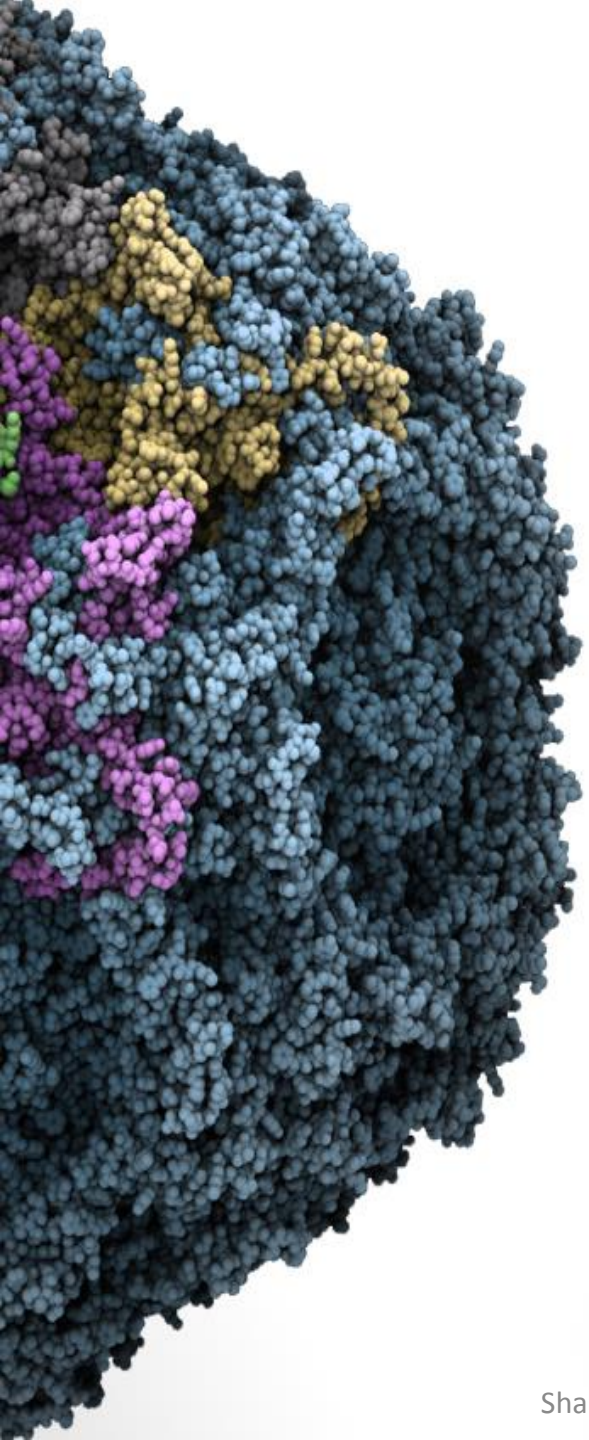
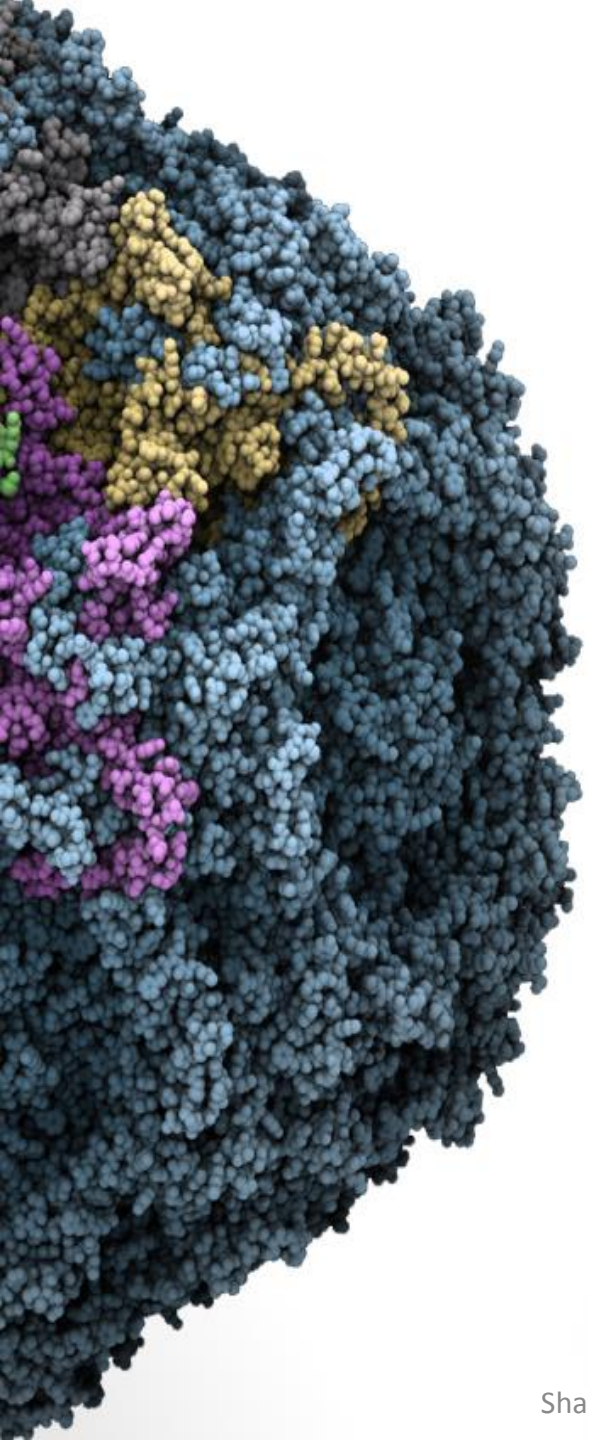


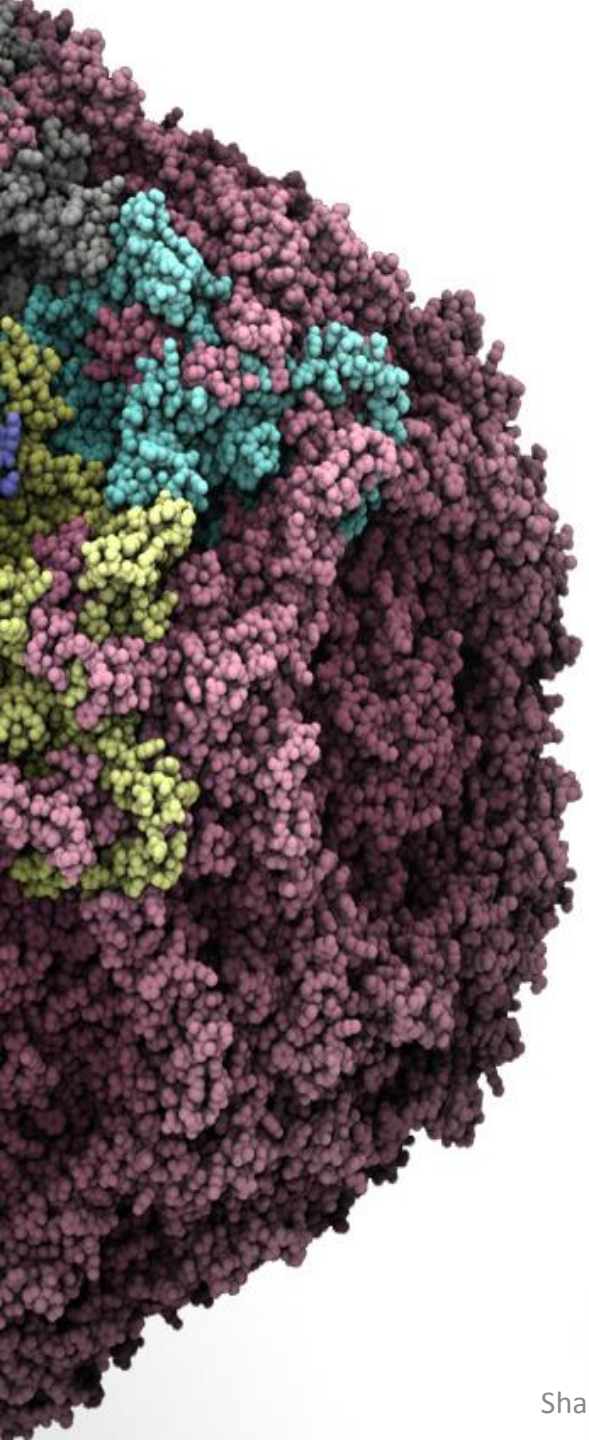
Parvovirus B19 and Cell Death

- Cell Death by B19V, apoptosis, necrosis, cell cycle arrest
- **Apoptosis**: 2 major pathways, **extrinsic** and **intrinsic**; both: activation of caspases.
- **Extrinsic**: ligation of death ligands (i.e Fas & TNF-α to death receptors (activation of caspases 8/10
- **Intrinsic** (mitochondrion): Bcl-2 (Bax, Bak) – **MOPS [29].**



Parvovirus B19 and Cell Death

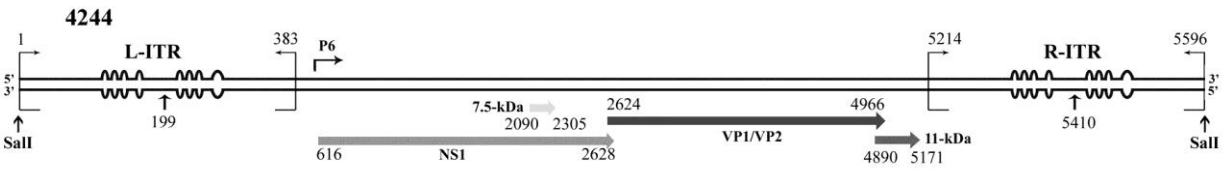
- **Necrosis**:
  - ❖ Organelle swelling
  - ❖ Mitochondrial membrane dysfunction
  - ❖ Massive oxidative stress
  - ❖ Rapid plasma-membrane permeabilization
- **Previously**: thought to be un-regulated cell death
- **Recently**: a number of regulated non-apoptotic cell death pathways **[29]**.



Parvovirus B19

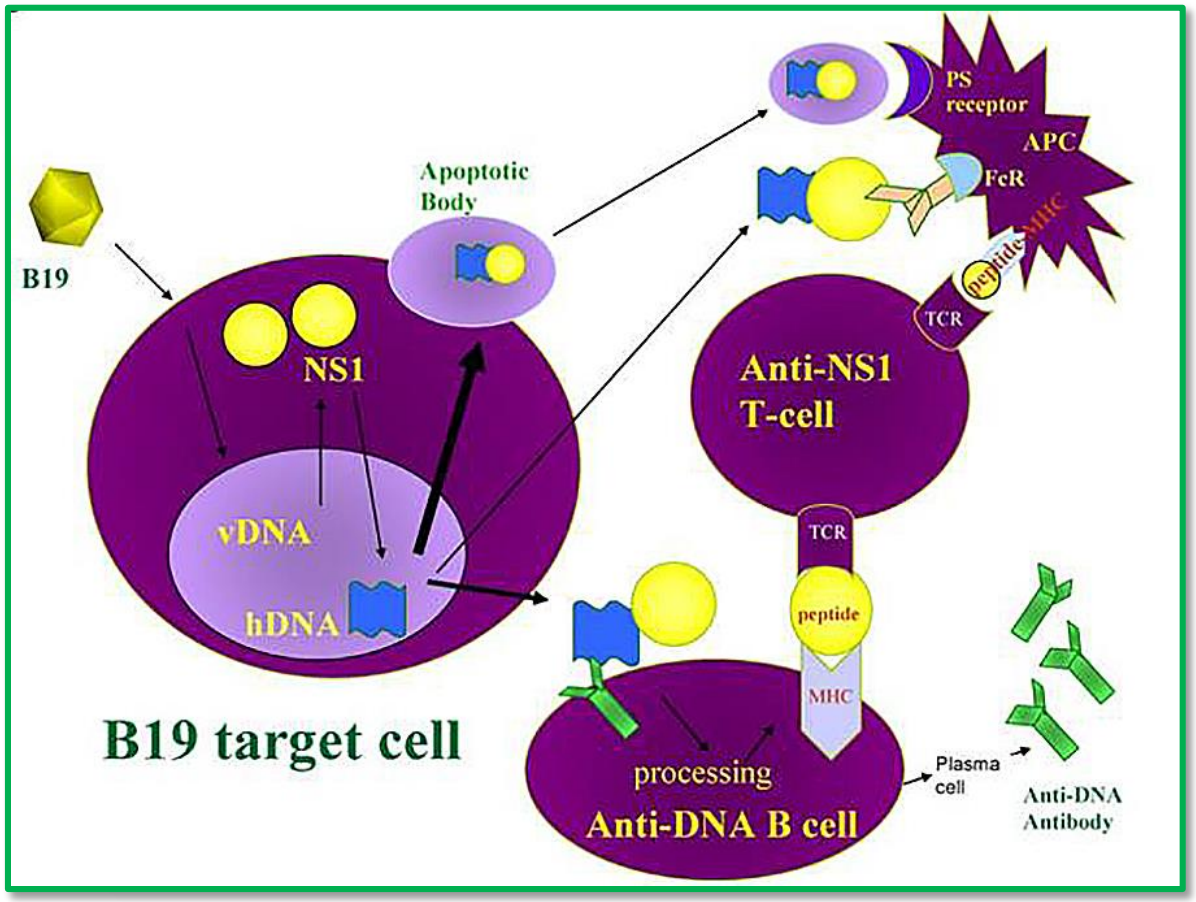
- Transcription of viral genome: single promoter (**p6**)
- P6: regulation of synthesis of all nine viral transcripts
- Non-spliced transcript: production of the nonstructural protein (**NS1**)
- Eight transcripts: two capsid proteins (**VP1** and **VP2**), **7.5** & **11-kDa** proteins **[23, 25]**

Parvovirus B19



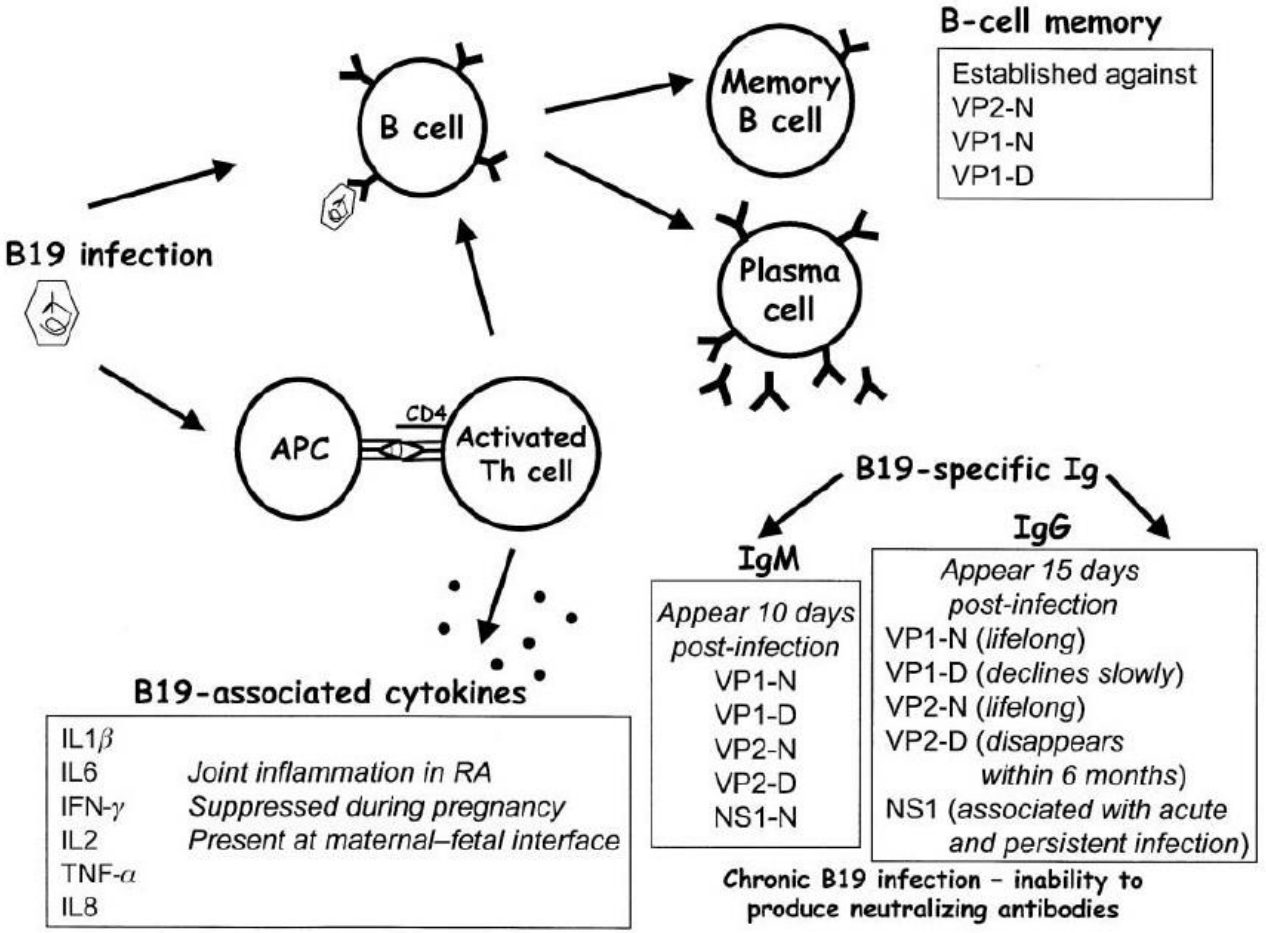
- **NS1** (Multifunctional Protein):
- ✓ Influencing the activity of other viral and cellular promoters **[28]**.
- ✓ Apoptosis (Connection btw **TNF-α** & **NS1** pathways)
- ✓ IL6 activation (**NF-κB**)
- ✓ G0/G1 arrest etc **[29]**.
- **VP1/2:** inhibiting colony formation of BFU-E cells **[30]**.

Parvovirus B19



http://www.medsci.org/v08p0088.htm

Parvovirus B19



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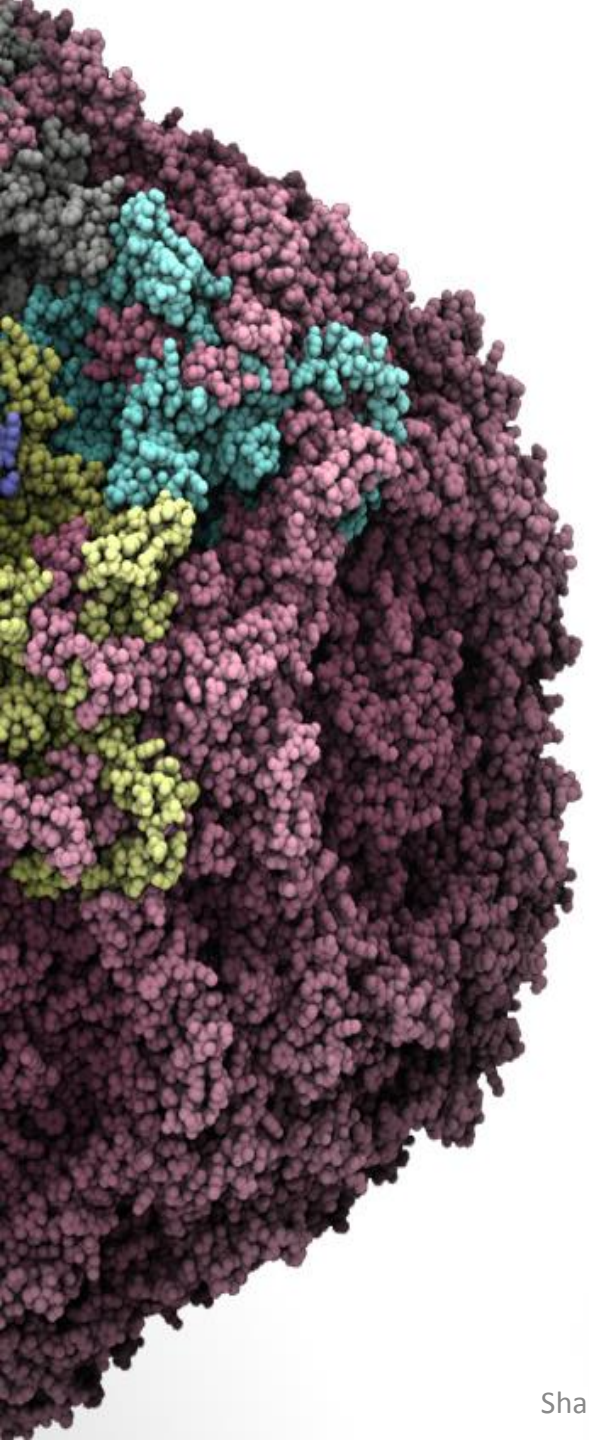
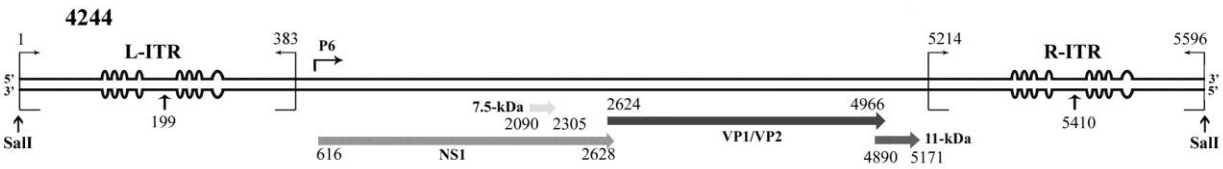


Parvovirus B19



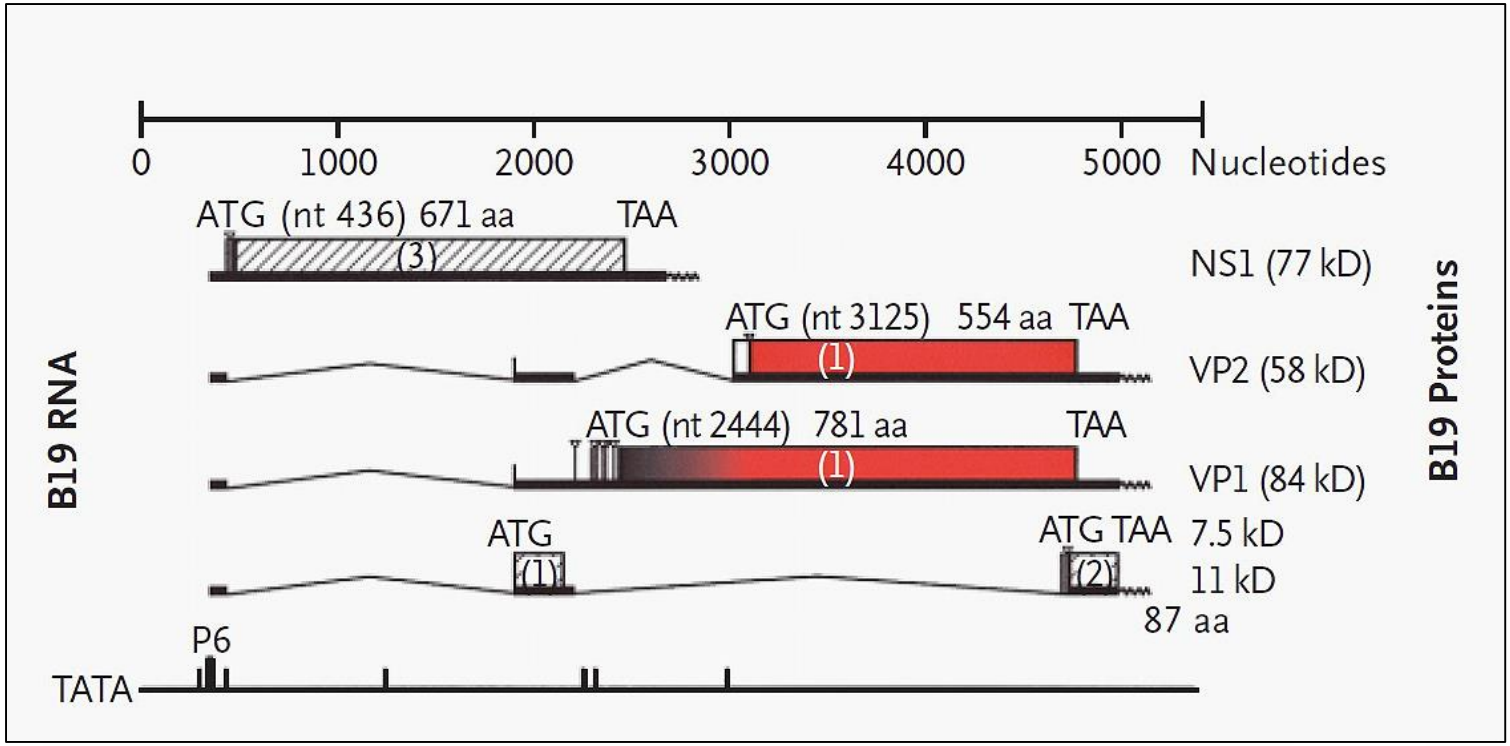
- **11-kDa Protein** (Proline-rich):
- Critical for:

  VP2 capsid production

  Trafficking in infected cells **[26]**.
- Apoptosis in EPC **more than NS1 [27]**.
- **Result:**

  Virus Replication and Infectivity **[26]**.
- **7.5 kDa Protein:** Unknown

Parvovirus B19



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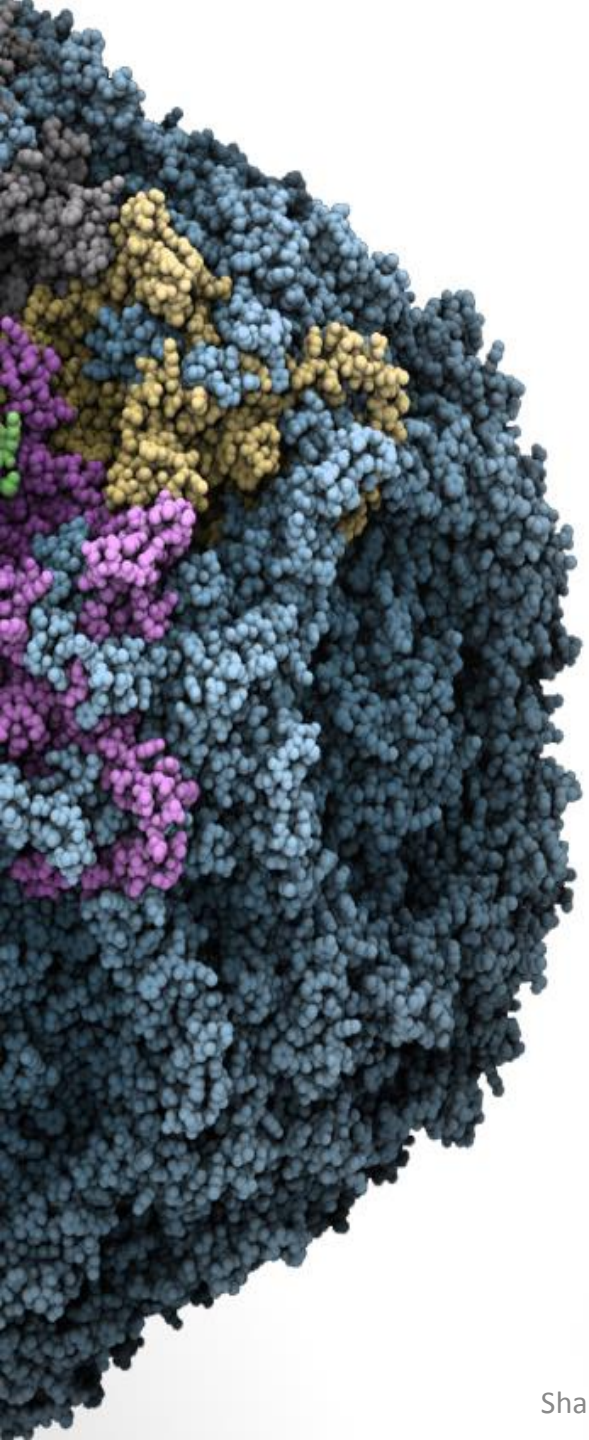

Parvovirus B19 and Leukemia

- Patient, **parvovirus**, **acute lymphoblastic leukemia**, remained parvovirus positive according (PCR testing) but **no clinical symptoms** for 27 months off chemotherapy **[20]**.

- A higher proportion of human parvovirus B19-positive cases in leukaemic patients **[21]**.

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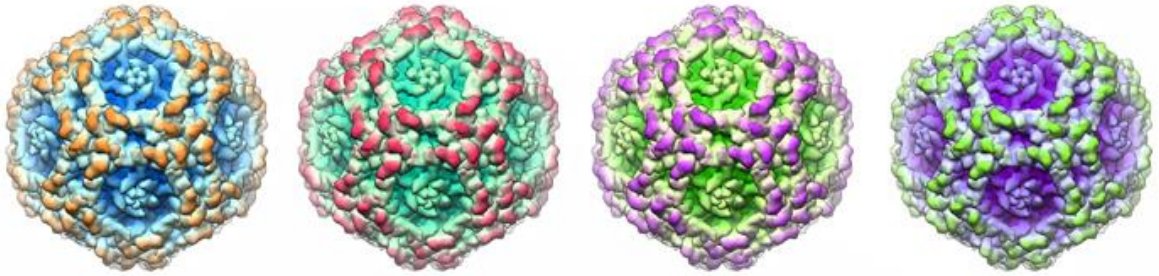

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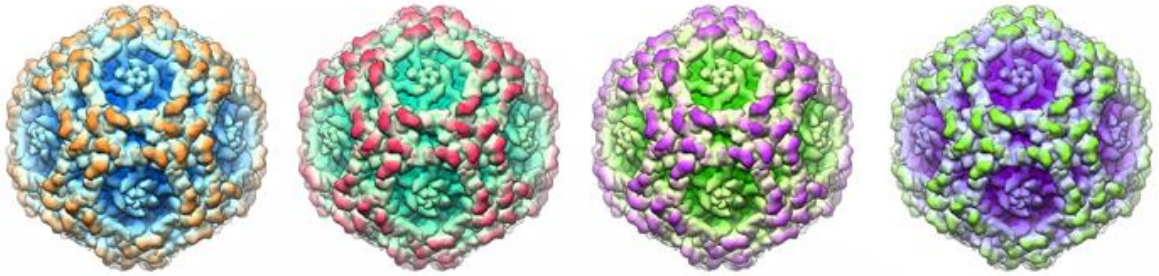

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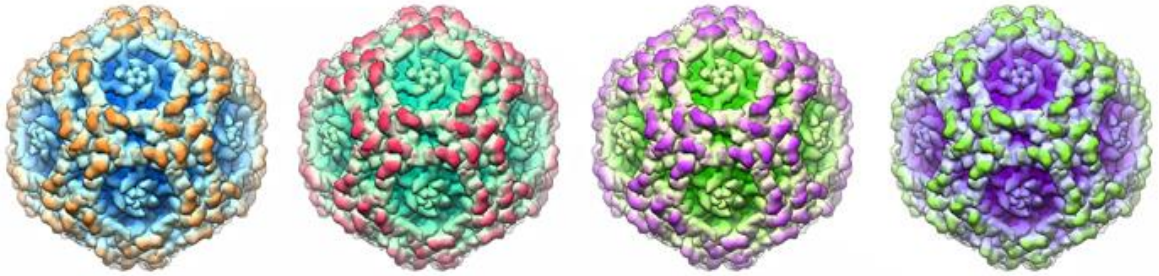

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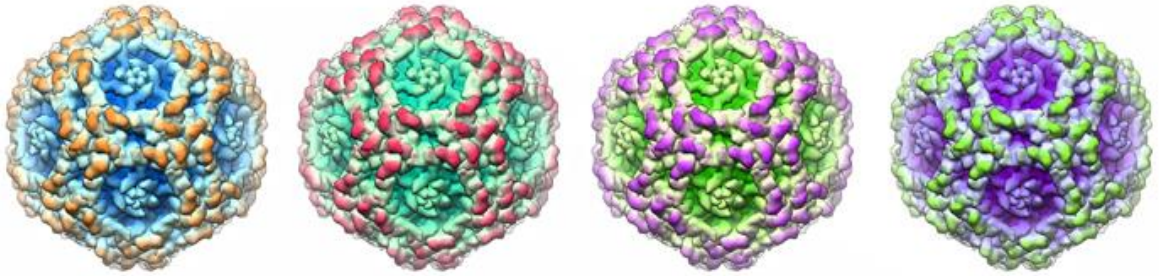

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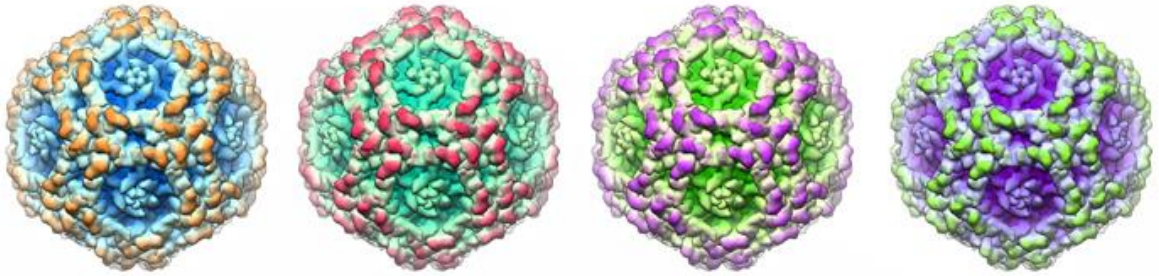

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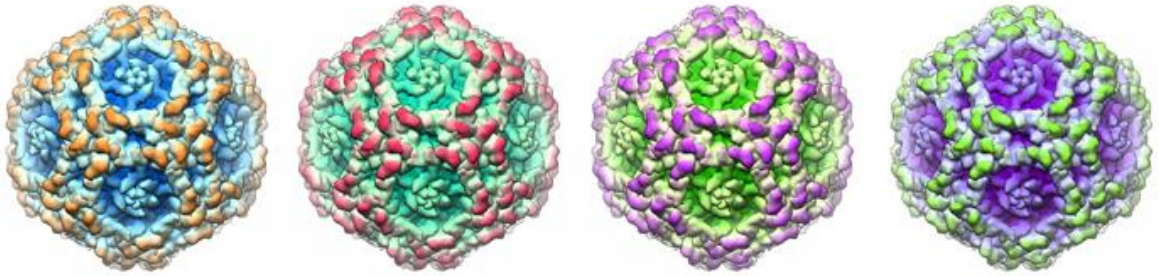

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